OFFICE OF SPECIAL MASTERS
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To Be Published

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PATRICK MULVANEY and CHRISTINE MULVANEY, as Parents and Natural Guardians of DANIEL C. MULVANEY,	*	
Petitioners,	*	
v.	*	Entitlement. MMR followed within two weeks by opsoclonus-myoclonus syndrome with pre-existing tumor (neuroblastoma); is MMR substantial factor in OMS
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *		

Anne C. Toale, Sarasota, FL, for petitioners
Glenn A. MacLeod, Washington, DC, for respondent

MILLMAN, Special Master

DECISION[1]

On May 17, 2005, petitioners filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that MMR vaccine, which their son Daniel Mulvaney (hereinafter, "Daniel") received on June 6, 2002, was a substantial factor in causing

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, petitioner has 14 days to identify and move to delete such information prior to the document's disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access.

opsoclonus-myoclonus syndrome[2] (hereinafter, "OMS") also known as Kinsbourne's disease, named after Dr. Marcel Kinsbourne who had written a medical article about the syndrome. Respondent denies petitioners' allegations, stating that Daniel's neuroblastoma[3] was the sole and sufficient cause of his OMS.

The undersigned had a hearing in this case on June 2, 2006. Testifying for petitioners were petitioner Patrick Mulvaney (Daniel's father) and Dr. Marcel Kinsbourne. Testifying for respondent was Dr. Michael H. Kohrman.

FACTS

Daniel was born on May 30, 1997. His mother had premature rupture of the membranes. Med. recs. at p. 1. He had respiratory distress syndrome. Med. recs. at p. 194.

Daniel had his first MMR vaccination as well as oral polio vaccine on June 2, 1998. Med. recs. at p. 18.

From March 9, 1999 to June 6, 2002, Daniel had 17 instances of cold, cough, pharyngitis, sinusitis, bronchitis, or upper respiratory infection (URI), or a combination thereof. Med. recs. at pp. 106, 144. The last two of those URIs occurred within weeks of his June 6, 2002 vaccinations. On April 29, 2002, Daniel had a cough and pharyngitis. Med. recs. at p. 143. On

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[2] Opsoclonus-myoclonus syndrome is "a syndrome of movements of the eyes (opsoclonus) and trunk (myoclonus), occurring in conjunction with a number of conditions, including viral infections, trauma, drug toxicity, tumors, and hyperosmolar nonketotic coma. It also occurs as a paraneoplastic syndrome...." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1827.

[3] Neuroblastoma is a "sarcoma consisting of malignant neuroblasts, usually arising in the autonomic nervous system (sympathicoblastoma) or in the adrenal medulla; it is considered a type of neuroepithelial tumor and affects mostly infants and children up to 10 years of age." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1253.

June 6, 2002, his medical records note that since his last visit, Daniel had an interim illness (undated) of a recent cough, croup, and pharyngitis. Med. recs. at p. 144.

Daniel received his second MMR vaccination (as well as DPaT and inactivated polio vaccines) on June 6, 2002 when he was five years old. Med. recs. at p. 18.

On June 17, 2002, Mrs. Mulvaney called Daniel's dentist to report that he fell and his upper lip was bleeding. Daniel tripped on the sidewalk. Med. recs. at p. 569. X-rays were taken that day. Med. recs. at p. 570.

Twenty days after vaccination, on June 26, 2002, Mrs. Mulvaney took Daniel to the doctor because he had been falling frequently for the prior five days. He fell the prior week and hit his teeth. He had a runny nose for three days. Med. recs at p. 146.

On June 27, 2002, a brain MRI showed no intracranial abnormality. Med. recs. at p. 212.

On June 27, 2002, Mrs. Mulvaney called the doctor, telling him that Daniel seemed much worse that day. He swayed when he walked, bumped into walls, would not walk by himself, and fell. Med. recs. at p. 148.

On June 28, 2002, Dr. Izak H. Kielmovitch consulted on Daniel's dizziness. He had an acute onset of disequilibrium four to five days previously, not associated with nausea or vomiting. Dr. Kielmovitch's diagnosis was most likely benign positional vertigo of infancy, which is a form of migraine. Med. recs. at p. 214.

On July 2, 2002, Daniel saw Dr. Ron Davis, a pediatric neurologist, who noted that for the last week to week and one-half, Daniel was unsteady. He fell two weeks earlier and hit his face. His hands shook. Med. recs. at p. 217.

On July 9, 2002, Daniel saw Dr. Davis, who noted significant ataxia. Med. recs. at p. 215.

On July 26, 2002, Dr. Davis diagnosed acute cerebellitis (a repeat MRI was negative). Med. recs. at p. 219.

On September 12, 2002, Mrs. Mulvaney telephoned the doctor to report a possible reaction to MMR vaccine. The VAERS form was completed and mailed September 16, 2002. Med. recs. at p. 158. The VAERS report states that onset was June 23, 2002. Med. recs. at p. 221.

On August 4, 1003, Daniel complained of a recent inability to swallow more solid food. Med. recs. at p. 170.

On August 7, 2003, Daniel saw Dr. Jasna Kojic, a pediatric neurologist. Daniel had a worsening of ataxia and a new onset of difficulty swallowing. Med. recs. at p. 239.

On August 13, 2003, an MRI of Daniel's abdomen showed a retroperitoneal mass medial to the right kidney measuring 5.1 cm x 3.7 cm x 2.8 cm. Med. recs. at p. 465.

On August 22, 2003, Dr. M. Joe Ma at Florida Hospital Pathology Department, reported a right retroperitoneal tumor excision. Daniel had a nodular retroperitoneal neuroblastoma with associated autonomic ganglia and peripheral nerves. Med. recs. at p. 241.

On September 11, 2003, Dr. Clifford A. Selsky noted that, with the excision of Daniel's neuroblastoma, his OMS resolved. Med. recs. at p. 249.

But, subsequently, after viral illnesses, the OMS returned in February 2004, according to Dr. Michael R. Pranzatelli in a record dated March 17, 2004. Med. recs. at p. 265. Dr. Pranzatelli saw Daniel at The National Pediatric Myoclonus Center. *Id.* Dr. Pranzatelli

examined Daniel and saw opsoclonus during tracking maneuvers. Med. recs. at p. 266. He had difficulty looking down. His stance was wide-based and he had an ataxic gait. Dr. Pranzatelli diagnosed OMS that was chronic and relapsing-remitting. *Id.* He also diagnosed possible attention deficit disorder, secondary to OMS. Med. recs. at p. 267. His impression was that Daniel has chronic paraneoplastic OMS of moderate or mild-moderate severity, with several relapses. *Id.* Daniel's lumbar puncture showed a cerebrospinal fluid (CSF) with a three-fold increase in B-cells and a two-fold increase in activated T-cells. Targeting the B-cells should help eliminate his tendency to relapse, and the most effective drug was Rituximab. *Id.* To help him remit neurologically, the most effective drug was ACTH. *Id.*

On April 2, 2004, Daniel saw Dr. Kojic. Intravenous immunoglobulin (IVIG) therapy every six to eight weeks did not dramatically improve Daniel's condition. Med. recs. at p. 268. She recommended Daniel see Dr. Pranzatelli, who recommended ACTH. Daniel continued to have ataxia and OMS. *Id.* Dr. Kojic concluded that Daniel had not shown marked improvement after removal of his neuroblastoma and several months of IVIG therapy. Med. recs. at p. 269.

From April 5 to 9, 2004, Daniel was hospitalized at Florida Hospital for ACTH treatment. Med. recs. at p. 271.

On June 9, 2004, Daniel saw Dr. Kojic. He had major improvement in OMS since starting ACTH. His family had not seen any myoclonus for at least the prior two weeks. He had no ataxia on physical examination. Med. recs. at p. 285.

On November 10, 2004, Daniel saw Dr. Pranzatelli. Med. recs. at p. 296. Daniel was doing great on Rituximab and ACTH. A repeat lumbar puncture showed elimination of CSF B-

cells and reduction in T-cell activation. The only remaining problem was elevated cytotoxic/suppressor T-cells.

Daniel's pediatrician Dr. Joseph F. Savona has a sheet in his pediatric records for Daniel entitled "Guidelines for Patients with OMS." Med. recs. at p. 20. The first guideline is that "no live virus vaccine should ever be used." *Id.*

Other Submitted Material

Petitioners filed Ex. B, Dr. Kinsbourne's seminal article on OMS, entitled, "Myoclonic encephalopathy of infants," 25 *J Neurol Neurosurg Psychiat* 271-76 (1962), in which he describes six children with OMS, one of whom had onset after DPT vaccination. Dr. Kinsbourne found it a "reasonable guess" that virus infections or immunization set up a self-perpetuating autoimmune process lasting for years. *Id.* at 276.

The undersigned filed as C. Ex. # 4 an article titled "The Immune System" from Dr. Pranzatelli's website: www.omsusa.org/pranzatelli-immune.htm. Under the subheading "What goes wrong in autoimmune disease?" Dr. Pranzatelli writes, at pages 5 and 6:

> An antigen may not stimulate an immune response unless *co-stimulation* has occurred.
>
> The main co-stimuli that empower an immune response are:
> - virus
> - tumor
> - vaccine

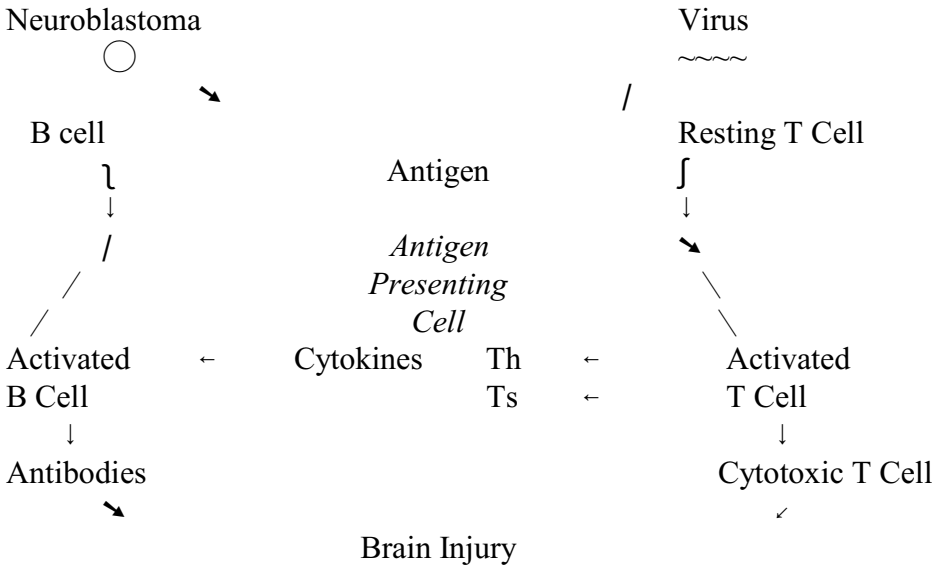
He continues, at page 6, under the subheading "How does the immune system fail in opsoclonus-myoclonus?"

> We believe the immune system fails twice. When neuroblastoma is the cause, the immune system allows the tumor to grow, then seems to overreact, and in the process injures the brain.

> Such confusion could happen in a number of ways. Tumor or viral antigens may resemble brain antigens enough to trigger cross-reactivity by a process called *molecular mimicry*. The immune system under stress might make such an error in genetically vulnerable children.
>
> Once triggered, antibodies, cell-mediated immunity, or both could deal the blows. ... We have proposed that T cells and cytokines may be instrumental to the autoimmune injury found in pediatric opsoclonus-myoclonus. Even if autoantibodies are involved, their production may require the collaboration of T cells. Our testable hypotheses of opsoclonus-myoclonus are diagrammed ... below.

Dr. Pranzatelli then includes a schematic that is difficult to reproduce on this page, but approximates the following dual process of autoimmune reaction resulting in brain injury:

Autoimmune Reaction



Petitioners' Ex. C is Dr. Pranzatelli's "Review. The Immunopharmacology of the Opsoclonus-Myoclonus Syndrome," 19 *Clin Neuropharm* 1:1-47 (1996). At page 2, Dr. Pranzatelli states:

> The etiologic association of OMS with a remote neoplasm (paraneoplastic) or a nonencephalitic viral infection (paraviral),

> each attributed to nearly half of the cases, is more common than rare cases caused by other acquired and genetic disorders. An immunogenic mechanism of OMS was suggested almost 20 years ago and recently has been gaining support. The fact that both a reaction to a tumor and to a virus could induce the same clinical syndrome in both infants and adults has presented both a puzzle and a clue.

He goes on to say, at page 4, "Clinically, the onset of symptoms usually follows a viral prodrome by several days, suggesting a para- or postviral process." He continues at pages 18,19, and 20:

> Environmental factors are likely to be very important in OMS, including infecting agents such as viruses or bacteria and **immunizations or vaccinations**. Assessment of the potential effects of immunization on the onset of OMS is not simple. Even at the mean age of onset of 18 months in pediatric OMS, most of the children will have had immunizations with diphtheria-pertussis-tetanus (DPT) or measles-mumps-rubella (MMR). Many parents relate the onset of OMS shortly after one such immunization. ... The immune mechanism may be a type II or type IV hypersensitivity reaction, incorporating evidence that autoantibodies alone seem insufficient to induce the syndrome without, presumably, a cellular immune (T-cell) response. ... In children, the immune system may become overactive because of the high frequency of viral infections, which average 10 or more yearly during infancy. **Immunizations, which precede the onset of OMS in some pediatric cases, may be another predisposing factor**. Immunizations, designed to "boost" the immune system against specific antigens, which are given repetitively and overlap with the mean age of onset of OMS, initially activate T cells (generalized activation). ... [Emphasis added.]

In concluding, Dr. Pranzatelli states, at page 36:

> An abnormality of both humoral and cellular immunity (i.e., both B cells and T cells) is the most attractive hypothesis based on current data available in OMS and abundant information on other autoimmune neurologic disorders. A peripheral induction mechanism involving molecular mimicry or one of several other possible mechanisms leads to immune system dysregulation, which transiently allows otherwise forbidden autoaggression against cross-reactive brain antigens. **[I]mmunizations are logical**

candidates for costimulation in peripheral induction in children.... [Emphasis added.]

TESTIMONY

Patrick Mulvaney testified first for petitioners. Tr. at 8. Daniel developed normally for his first five years and kept up with his older brother. Tr. at 9. On June 6, 2002, he received MMR, DPaT, and polio vaccines. Tr. at 10. He began to stumble, trip, and fall, showing a lack of coordination. *Id.* Eleven days later, he fell and hit his teeth on the concrete. Tr. at 11-12. He saw his pediatrician to receive five to six stitches in his head. Tr. at 11.

On April 29, 2002, Daniel had a viral infection (pink throat, 99-102° temperature for six days, wet cough) and was diagnosed with pharyngitis. Tr. at 16. This was six weeks prior to his vaccinations on June 6, 2002. Daniel had another viral illness on June 23, 2002, three weeks after his vaccination, with a runny nose for three days and a croupy cough. Tr. at 20. Between his April 29, 2002 croup and his June 6, 2002 vaccinations (when he was healthy), he had a recent cough, croup, and pharyngitis. Tr. at 30.

Dr. Marcel Kinsbourne testified next for petitioners. Tr. at 33. He has practiced pediatric neurology. Tr. at 34. In 1957, he saw children with OMS. He saw six children all diagnosed with cerebellar ataxia who did not improve. They had myoclonic shocks where the muscle suddenly jerks. Tr. at 36. He wrote an article about this in 1962, and myoclonic encephalopathy of infants became known as Kinsbourne disease. Tr. at 37. Opsoclonus may happen sooner or later. *Id.* Three of these six children had recent viral infections and one had a DPT vaccination. Tr. at 38. There was an autoimmune attack on the cerebellum. *Id.* Treatment of an immune-mediated disorder is with ACTH. Tr. at 39. These six cases were not neuroblastoma cases. *Id.*

When the ACTH was halted, the jerks came back. *Id.* The same thing happens with neuroblastoma. Tr. at 39-40. Treatment with ACTH must continue for three years. Tr. at 39.

Daniel had unsteadiness, falling on June 17, 2002, two weeks after his MMR on June 2, 2002. Tr. at 40. He had an apparent viral infection six to seven weeks earlier and a more recent viral infection after that one. Tr. at 41. Myoclonus comes on very abruptly. *Id.* Daniel was initially diagnosed with cerebellar ataxia, but he did not improve. *Id.* Daniel had dancing eye syndrome. *Id.* The doctors discovered a neuroblastoma nestled behind his peritoneum and excised the neuroblastoma. Tr. at 41-42. Daniel's OMS got better, but came back. Tr. at 42. He does not have OMS any more but does have learning disabilities, which is typical of OMS. *Id.*

Neuroblastoma is the most common tumor outside the head in children. Tr. at 43. The nerve cells destined to form the sympathetic nervous system instead form the tumor. *Id.* It can go away without therapy. *Id.* It can also regress but no one knows why. *Id.* OMS is extremely rare in neuroblastoma. Tr. at 44. Only one to three percent of neuroblastoma cases have OMS. *Id.*

Dr. Kinsbourne testified that Daniel has a dysfunctional immune system because of his various infections. Tr. at 45. While only three percent of children with neuroblastoma have OMS, 20 to 50 % of OMS children have neuroblastoma. Tr. at 49. OMS recurs in two-thirds of the cases where the child's neuroblastoma has been excised. Tr. at 53. OMS is not different whether a virus or a tumor causes it. Tr. at 55. Both paths lead to the same disorder. *Id.*

Dr. Kinsbourne's opinion in this case is that MMR played a role. *Id.* As Dr. Pranzatelli stated, you can have an immune reaction against an antigen such as a tumor antigen. Tr. at 56.

But in order to get antigenic spreading or epitope spreading so the immune system also attacks itself, i.e., self-antigens, you need a coactivating influence, in other words, a double hit. *Id.* On the one hand, the body has to be generating an immune response. *Id.* On the other hand, something else has to upregulate it, to overstimulate it to make it intense enough to cause serious damage to the brain. *Id.* Dr. Kinsbourne believes that this is what happened to Daniel. He very likely had the neuroblastoma before the vaccination and was responding to it immunologically. *Id.* But until the MMR was administered, that immune reaction to the neuroblastoma had not spread out to attack Daniel's natural cells. *Id.* After the MMR was given, the vaccine upregulated cytotoxic T-cells which attacked antigens other than the specific initial antigen to which his immune system had responded, causing this paraneoplastic syndrome (OMS). Tr. at 56-57.

In the case of neuroblastomas, the question is why are neuroblastomas so common yet OMS so rare? Tr. at 57. If neuroblastomas are sufficient to cause OMS by themselves, why do they not do so more often? *Id.* That distinction is why Dr. Pranzatelli writes, and Dr. Kinsbourne agrees, that there has to be some coactivation, i.e., something else besides the neuroblastoma that happens to the child that raises the level of his body's immune response where it begins to attack itself. Tr. at 57-58.

Someone can get an immune reaction from an attenuated virus just as much as from a wild virus, and MMR has three viruses that entered Daniel's body which, in Dr. Kinsbourne's opinion, overreacted. Tr. at 58. A period of two weeks from MMR vaccine to onset of OMS is classic for an autoimmune reaction. Tr. at 62, 75. Daniel's prior viruses occurred too long before the onset of his OMS to be causative, and the other viruses he had did not stimulate him.

Tr. at 62. Had it not been for MMR vaccine, Daniel would not have had OMS or he would not have had it at that time. Tr. at 63. He was at risk for developing OMS because he had a neuroblastoma and because of the nature of his immune system. *Id.*

Both B-cells and T-cells are involved. Tr. at 67. Daniel was given Rituximab to down-regulate his B cells. Tr. at 68. He was given ACTH to deal with his T-cells. *Id.* IVIG (intravenous immunoglobulin) was administered to Daniel to downregulate Daniel's immune system because it was overactive. Tr. at 68-69. OMS is an autoimmune disease. Tr. at 69. Petitioner's Ex. K shows that immunizations can worsen OMS. Tr. at 71. Daniel's OMS was subclinical and the MMR vaccine made it clinical. Tr. at 72. Petitioner's Ex. C, p. 19, shows that autoantibodies seem insufficient alone to induce OMS without a T-cell response (MMR caused the T-cell response). Tr. at 73.

Daniel did not suffer OMS after his first MMR vaccination. Tr. at 76. After having OMS subsequent to his second MMR, he had recurrent episodes of OMS due to viral infections. *Id.* But Daniel's numerous childhood illnesses did not trigger the OMS. *Id.* Daniel's prior infections could have contributed to his OMS if they had occurred in the relevant time frame, but it is not exactly clear when they happened. Tr. at 77. Daniel's neuroblastoma pre-existed the MMR of June 6, 2002. *Id.* Upwards of 50% of OMS is associated with neuroblastoma. *Id.* None of Daniel's treating doctors associated his MMR with his OMS. Tr. at 78. Dr. Pranzatelli is one of the leading experts in OMS. *Id.* Dr. Kinsbourne's opinion is that MMR in combination with the pre-existing neuroblastoma caused Daniel's OMS. Tr. at 83-84.

Dr. Michael H. Kohrman, a pediatric neurologist, testified for respondent. Tr. at 86. His opinion is that MMR was not a substantial factor in causing Daniel's or any other child's OMS.

Tr. at 87. It is well-known paraneoplastic syndrome. Nine to 18% (higher than 3%), according to Dr. Pranzatelli's website, of neuroblastoma patients have OMS. Tr. at 87-88. Thus, OMS is a reasonably common complication of neuroblastoma. Tr. at 88. Doctors often see OMS in the absence of any other illness. *Id.* Dr. Kohrman stated that many pediatric neurologists believe that almost all cases of OMS are related to occult neuroblastoma. *Id.* It may take years to find the tumor. *Id.* He thinks that OMS is a natural result of neuroblastoma. Tr. at 89.

Any time one stresses the immune system, one will often see relapses and exacerbation of OMS. *Id.* Antigenic stimulus does not bring on the OMS although it may bring it to light, but it is going to be there anyhow. *Id.* Whether the antigenic stimulus brings out the OMS today or the OMS comes out with the next viral infection, it does not mean that the antigenic stimulus is the cause of the OMS. It is the neuroblastoma that sets up the child for OMS. Tr. at 90. The antigenic stimulus of Daniel's OMS could have been croup a month earlier and then a second antigenic stimulus to make the OMS clinical. *Id.* Antigenic stimulus is a hypothesis and not proven. *Id.* Neuroblastomas with OMS may have a different pathology than neuroblastomas without accompanying OMS. Tr. at 91. We do not know the cause of OMS and there could be more than one cause. Tr. at 94.

Dr. Kohrman does not believe that MMR was a substantial factor in this case. *Id.* Daniel had his first MMR at a young age and he should have had a memory response. Tr. at 95. He should have had antibody production before two weeks, and two weeks is classic after the first MMR. *Id.* After the second MMR, one would expect a faster response. *Id.* If Daniel's second MMR triggered his OMS, Dr. Kohrman would have expected OMS to manifest sooner than two

weeks, sooner than five days. Tr. at 95-96. (Dr. Kinsbourne stated that the response varies. Tr. at 96.)

Dr. Kohrman stated that 90% of children produce a response to their first MMR. *Id.* We give a second MMR to ensure the response and to rechallenge the immune system. Tr. at 97. (Dr. Kinsbourne stated that just because Daniel did not have a fever or rash reaction to MMR does not mean Daniel did not have an immune response to it. Tr. at 100. A response of a rash or fever is irrelevant because they are due to a cytokine response. An immune response is due to T-cells. One cannot make any inference about Daniel's T-cell response to MMR from his lack of a rash or fever. Tr. at 102.) Dr. Kohrman stated that the response of T-cells, B-cells, and cytokines is intimately related. Tr. at 103. OMS is an antibody response. *Id.* In OMS, an antibody attacks the Purkinje cells[4] in the nervous system, which has a huge B-cell component. *Id.* The key is that there is no definitive link between MMR and OMS. Tr. at 104. Dr. Kohrman reiterated that there is no clear link that MMR is necessary as a stimulus to cause OMS. *Id.* OMS often occurs on its own without a preceding viral infection. *Id.*

Dr. Kohrman stated it is no more likely that MMR caused Daniel's OMS than his croupy viral infection a month earlier or a viral infection six months earlier. Tr. at 106. Because Daniel had a documented neuroblastoma, that is sufficient in and of itself to produce the entire OMS. *Id.* The cause of OMS probably has to do with host factors and not necessarily another viral or immune stimulus. Tr. at 107. It has to do with the host's ability to process the tumor, or some difference in tumor biology. *Id.*

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[4] Purkinje cells are "large neurons in the cerebellar cortex that have piriform cell bodies in the Purkinje layer ... and large branching dendrite trees going through the outer (molecular) layer towards the surface." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 325.

Dr. Kohrman does not think that Daniel has a dysimmune immune system. Tr. at 108. Twenty infections in two years of life is well within normal limits. *Id.* Any time one challenges the immune system, the immune system is upregulated. Tr. at 109. OMS stresses an injured nervous system. Tr. at 110. OMS is the result of injury by the autoantibody to the nervous system itself. *Id.* The neuroblastoma causes the autoantibody. *Id.* The cerebellum produces most of the clinical symptoms. Tr. at 111. After Daniel's neuroblastoma was removed, viral infections stressed his nervous system and brought back the symptoms of OMS. *Id.* The infection may produce an antibody response which upregulates the immune system in general, and more of the antibody against the Purkinje cells. *Id.* The B-cells can produce an antibody which produces the injury. The T-cells regulate the B-cell response. Tr. at 113. There can be subclinical OMS if the antibodies are at a low enough level. *Id.*

Daniel's neuroblastoma measured 5 cm and had been growing from two to four years. Tr. at 113-14. One can see OMS with either microscopic or a very large neuroblastoma; it all depends on the host and maybe the tumor itself. Tr. at 114. The manifestation of OMS depends on when there is a significant antibody response to produce symptoms. Tr. at 115.

Dr. Kohrman stated that MMR vaccine was possibly a factor (but not a cause) that contributed to making Daniel's OMS clinical by non-specifically upregulating his immune system. Tr. at 116. It could have been a trigger as his viral infections could have been. *Id.* This is not an all or none phenomenon. Tr. at 117. It is probably a stepwise process. *Id.* Dr. Pranzatelli estimates there are 100-200 cases of OMS a year associated with neuroblastoma. Tr. at 118. In the last 40 years, since Dr. Kinsbourne described the syndrome, there would be 4,000-5,000 cases of OMS. *Id.* If MMR or other vaccinations were substantial factors in this process,

we should have seen multiple case reports of the vaccinations related temporally to OMS, and that has not happened. Tr. at 118-19.

Dr. Kinsbourne testified on rebuttal. Tr. at 126. He said there are many causes for autoimmune reactions. *Id.* With a neuroblastoma, we do not often know what the co-stimulus is, but in Daniel's case, we do know. *Id.* Daniel's earliest documented infection was six weeks before. *Id.* Another infection happened in the interim before vaccination, but we do not know when. *Id.* MMR is a reasonable mechanism. Tr. at 127. When Dr. Kohrman said that the MMR might have raised the level of Daniel's immune response to clinical symptoms of OMS, that is what Dr. Kinsbourne calls causation. *Id.* MMR is a substantial contributing factor. *Id.* Any role that other viral infections might have had is secondary. *Id.* Once the MMR had upregulated Daniel's immune response against his brain to a clinical level, his immune response, being higher, was more susceptible to the further effect of subsequent infections, leading to relapses of his OMS. Tr. at 128. MMR is engineered to challenge the immune system and is supposed to last for years or decades. Tr. at 129.

Dr. Kohrman stated we are assuming that MMR produces a second hit when OMS does not require a second hit to manifest itself. Tr. at 138-39. He thinks Daniel's croup was a more significant antigenic stimulus than the MMR because Daniel got better from the croup and we do not know that MMR produced any immune response. Tr. at 139-40. A normal response to MMR is upregulation of the immune system. Tr. at 140. That is what all viruses and infections do: they upregulate the immune system. Tr. at 140-41.

In Daniel's case, his autoimmune disease is the combination of his and his tumor's producing a cross-reacting antigen to his brain. Tr. at 142. It is a host and tumor effect, not a

viral effect. *Id.* Dr. Kinsbourne stated that some cases of OMS happen in the absence of documented costimulation. Tr. at 145. The appearance of documented costimulation makes the appearance of OMS more likely. Tr. at 146.

Dr. Kohrman said doctors typically do not look for two reasons for the same disease in a patient (Occam's razor or the principle of a single cause). *Id.* Actually, OMS probably saved Daniel's life because it identified a neuroblastoma which his doctors then removed before it had a chance to metastasize. Tr. at 146-47. As for Dr. Kinsbourne's point that if neuroblastoma were sufficient to cause OMS by itself, we would see more OMS among neuroblastoma children, Dr. Kohrman disagreed. Tr. at 148. Not all neuroblastomas have antigens that cross-react with Purkinje cells. *Id.*

DISCUSSION

To satisfy their burden of proving causation in fact, petitioners must offer "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Secretary of HHS, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" the logical sequence being supported by "reputable medical or scientific explanation[,]" *i.e.*, "evidence in the form of scientific studies or expert medical testimony[.]"

In Capizzano v. Secretary of HHS, 440 F.3d 1317, 1325 (Fed. Cir. 2006), the Federal Circuit said "we conclude that requiring either epidemiologic studies, rechallenge, the presence

of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in Althen...."

Close calls are to be resolved in favor of petitioners. Capizzano, supra, at 1327; Althen, supra, at 1280. *See generally*, Knudsen v. Secretary of HHS, 35 F.3d 543, 551 (Fed. Cir. 1994).

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, supra, at 1149. Mere temporal association is not sufficient to prove causation in fact. Hasler v. US, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984).

Petitioners must show not only that but for the vaccine, Daniel would not have had OMS, but also that the vaccine was a substantial factor in bringing about his OMS. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, supra, 418 F.3d at 1278; Grant, supra, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, supra, 35 F.3d at 548-49). To the undersigned, medical probability means biologic credibility or plausibility rather than exact biologic mechanism. As the Federal Circuit stated in Knudsen:

> Furthermore, to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program. The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal "compensation program" under which awards are to be "made to vaccine-injured persons quickly, easily, and with certainty and generosity." House Report 99-908, *supra*, at 3, 1986 U.S.C.C.A.N. at 6344.

> The Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.

35 F.3d at 549.

The Federal Circuit stated in Althen, supra, at 1280, that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."

As the Federal Circuit stated in Knudsen, supra, at 548, "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules." The undersigned's task is to determine medical probability based on the evidence before the undersigned in this particular case. Althen, supra, at1281 ("judging the merits of individual claims on a case-by-case basis").

The Federal Circuit in Knudsen, supra, at 549, also stated: "The special masters are not 'diagnosing' vaccine-related injuries."

As for epidemiological support for causation, the Federal Circuit in Knudsen ruled for petitioners even when epidemiological evidence directly opposed causation from a vaccine. In Knudsen, even though epidemiological evidence supported the opposite conclusion, i.e., that viruses were more likely to cause encephalopathy than vaccinations, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by

> a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

Dr. Kinsbourne, for whom Kinsbourne syndrome (another name for OMS) is named, opined that Daniel's neuroblastoma, although a cause of his OMS (which occurs in a minority of neuroblastoma cases), was not the only cause of his OMS. Daniel's second MMR, containing three live, though attenuated, viruses, provided the antigenic challenge that stimulated his T-cells and B-cells to bring the OMS out clinically. This is his medical theory, the first Althen prong.

The logical sequence of cause and effect, according to Dr. Kinsbourne, is that an antigenic stimulus in a susceptible individual such as Daniel can and did produce an autoimmune disease such as OMS. Dr. Kinsbourne testified that MMR was a substantial factor in triggering Daniel's OMS and without the MMR, Daniel would not have had OMS. This is the second Althen prong.

The timing here is medically appropriate for an immune response to MMR vaccine. Two weeks is a classic response time for an adverse reaction, as Dr. Kinsbourne stated. That Daniel did not manifest a fever or rash after MMR did not mean the vaccine had no immune effect. If Daniel had a cytokine response to the MMR, he would have had rash and/or a fever. But, instead, Daniel had a T-cell response to the MMR, triggering the OMS, or making the OMS clinical. This is the third Althen prong.

Dr. Kohrman's objection that Daniel could not have had an adverse reaction to his second MMR fails to take into account that an adverse reaction consisting of stimulation of T-cells is not dependent on a cytokine reaction that produces a fever and/or rash. He admitted in his testimony

that MMR could have had a triggering effect, but would go no further. To Dr. Kohrman, trigger does not mean causation. To Dr. Kinsbourne, trigger does mean causation. Legally, if the trigger is a substantial cause, that is all petitioners need to prevail.

Dr. Kinsbourne subscribes to the "two-hit" understanding of OMS, i.e., that Daniel's neuroblastoma was not the only substantial factor causing Daniel's OMS. He needed another upregulation of his immune system and MMR vaccine provided that upregulation in order to trigger his OMS. This medical theory is consistent with the writings of the leading expert on OMS, Dr. Michael Pranzatelli, who is also a treating doctor for Daniel. Dr. Pranzatelli uses the term "costimulation" instead of "second hit."

Dr. Pranzatelli posits in his article that is petitioners' Ex. C that immunizations are logical candidates for costimulation in peripheral induction in children with OMS. That Dr. Pranzatelli posits costimulation of the immune system as a cause of OMS lends credence to Dr. Kinsbourne's "two-hit" medical theory of causation, and makes Dr. Kohrman's "Occam's razor" analysis (where only one cause is needed) less credible in this case.

Dr. Pranzatelli emphasizes that once a child has OMS, that child should not receive multiple vaccines of live viruses and should not be exposed to viral infections because live-virus vaccines and viral infections may worsen the child's OMS. We can see that, after Daniel's onset of OMS, whenever he had a virus, his OMS worsened.

Daniel was exposed to viral infections and the three attenuated viruses in MMR vaccine in April through June 2002 besides having neuroblastoma which itself can cause OMS. The Federal Circuit stated that close calls are to be resolved in favor of petitioners. Capizzano, supra, at 1327; Althen, supra, at 1280. *See generally*, Knudsen, supra, at 551. The nation's expert on

OMS posits that immunizations can costimulate the immune system, leading to OMS. The doctor for whom OMS is popularly named (Dr. Kinsbourne) testified that OMS is a two-hit illness, neuroblastoma being the first hit for Daniel and MMR being the second hit. Daniel's numerous viral infections did not seem to have the same costimulus effect during the two to four years that the neuroblastoma was developing since Daniel did not manifest OMS after any of those infections. Then Daniel received MMR and, within a medically appropriate time frame, he began to manifest signs of OMS.

Dr. Kinsbourne testified that MMR was a substantial factor in causing Daniel's OMS. In Shyface, supra, the Federal Circuit emphasized that the vaccine does not have to be the predominant factor in order for petitioners to prevail. In that case, the Federal Circuit held that both DPT vaccine and E. coli infection were substantial factors in causing Cheyenne Shyface's high fever which led to his death. Shyface, supra, at 1353 ("although the Shyfaces did not prove that the DPT vaccine was the only or predominant cause of his death, the requirements of the Vaccine Act are met *prima facie* upon proof of the substantial factor criterion.").

In Zatuchni v. Secretary of HHS, No. 94-58V, 2006 WL 1499982, at *5 (Fed. Cir. Spec. Mstr. May 10, 2006), the special master held that, although smoking was the primary cause of petitioner's decedent's death, her vaccine-induced fibromyalgia was a substantial factor in causing her death because it prevented her from exercising, and held that petitioner was entitled to the $250,000 death award.

In the instant action, we have at least two substantial factors, the neuroblastoma and the MMR vaccine, that caused Daniel's OMS. The viral infections, one occurring six weeks before administration of the MMR and the other some unspecified time closer to the administration of

the MMR, are unknown in terms of their immune effect. Perhaps they also challenged Daniel's immune system, but no expert herein could offer more than speculation as to their role. Dr. Kohrman opined that the viruses as well as the vaccine could have had an effect, but that the neuroblastoma alone caused the OMS.

The undersigned views Dr. Pranzatelli as more expert in OMS and its causes than Dr. Kohrman. Dr. Kinsbourne's testimony is consistent with Dr. Pranzatelli's explanation of OMS and its causes in his medical articles and website since Dr. Kinsbourne's two-hit analysis dovetails with Dr. Pranzatelli's costimulation understanding of the OMS process.

The undersigned holds that MMR was a substantial factor in causing Daniel's OMS and, but for the MMR, Daniel would not have had OMS.

Petitioners have prevailed in proving that MMR caused Daniel's OMS.

CONCLUSION

Petitioners are entitled to reasonable compensation. The undersigned hopes that the parties may reach an amicable settlement, and will convene a telephonic status conference soon to discuss damages and the means to achieve a damages resolution.

IT IS SO ORDERED.

July 31, 2006
DATE

s/ Laura D. Millman
Laura D. Millman
Special Master